Interdepartmental Conference

FROM THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, SCHOOL OF MEDICINE

Diagnosis of Obstructive Jaundice

MODERATOR: JAMES S. CLARKE, M.D.
DISCUSSANTS: PETER BARRETT, M.D., ERIC W. FONKALSRUD, M.D., JOHN N. JOHNSON, M.D., WILLIAM P. LONGMIRE, JR., M.D., MARTIN A. POPS, M.D., JOSEPH RÖSCH, M.D., RICHARD J. STECKEL, M.D., AND MILO M. WEBBER, M.D.

This is the edited transcription of an Interdepartmental Clinical Case Conference arranged by the Department of Surgery, University of California, Los Angeles, School of Medicine.

■ *The diagnosis of obstructive jaundice remains difficult yet vital, since operative decompression may relieve extrahepatic blockage, but operation can only harm patients with intrahepatic block or parenchymal cell inflammation or necrosis. Three new diagnostic methods (liver scanning, angiography, and transjugular transhepatic cholangiography) are reviewed, as is bilirubin metabolism, so important in the diagnosis of jaundice. Three clinical problems are discussed: extrahepatic obstruction due to cancer of the pancreas, biliary atresia causing jaundice in the newborn, and the diffuse ductal obstruction known as sclerosing cholangitis.*

An accurate diagnosis can usually be made with standard diagnostic techniques, such as history, physical examination and biochemical tests, and, when appropriate, gastrointestinal x-ray studies, cholecystography and cholangiography, liver biopsy, observation of the patient's course, and the three new radiological approaches mentioned above. Extrahepatic obstructive jaundice is an indication for surgical treatment, except perhaps in cases of sclerosing cholangitis.

DR. JOHN N. JOHNSON (Department of Medicine): The patient was a 24-year-old Caucasian male welder who was admitted to UCLA on October 11, 1966 with chief complaint of easy fatigability, weight loss, and some abdominal pain approximately two and a half months before admission. He had been well until that time. These symptoms were progressive, and approximately two and a half weeks before admission were accompanied by nausea, vomiting and the passing of light-colored stools. About a week before admission the patient's complexion became yellow and he noticed a lightening in the color of his stools and a deep yellow color in his urine.

His past history was relatively uncomplicated. On physical examination the positive findings included pronounced scleral icterus. The heart and lungs were within normal limits; the abdomen was soft; the liver was palpable approximately 3.5 cm from the right costal margin and was very tender. No other masses or organomegaly were noted. Bowel sounds were normoactive. A stool was noted to be light-clay colored. There was no ascites. With the exception of the jaundice, the remainder of physical examination was within normal limits.

Leukocytes numbered 12,000 per cu mm, the hematocrit was 45, and hemoglobin was 15.4 grams per ml. Other pertinent laboratory data included an alkaline phosphatase value of 21, bilirubin of 7.4, SGOT of 240, SGPT of 272. Prothrombin time was 85 percent, heterophile 1:7, negative ANA. An upper gastrointestinal x-ray series suggested effacement of the second portion of the duodenum.

The initial diagnosis was infectious hepatitis. After an appropriate period of hospitalization, it became evident that the response was not of infectious hepatitis, but more suggestive of an obstructive type of jaundice.

On November 22, a transjugular cholangiogram showed a dilated common bile duct. Because of this finding, an exploratory laparotomy was performed, and a hard tumor mass was found at the head of the pancreas. The liver was noted to be studded with metastatic lesions. Pathology report verified adenocarcinoma of the pancreas.

Cholecystojejunostomy and jejunojejunostomy were performed, and the patient's postoperative course was uncomplicated. However, his enzymes continued to increase and bilirubin to rise. He was discharged in December of that year to a nursing home.

Reprint requests to: Department of Surgery, UCLA School of Medicine, Center for the Health Sciences, Los Angeles, Ca. 90024 (Dr. Clarke).

DR. JAMES S. CLARKE (Department of Surgery): Moynihan said in 1926 that "no one living is infallible in the differential diagnosis of obstructive jaundice."[8] Today, this statement stands as a question—is it still true, or only an interesting historical relic?

By way of giving some perspective to the presentations which follow I wish to comment briefly on the selectivity exercised in developing the program of this conference. Of the many ways of approaching the diagnosis of a patient with jaundice, we have chosen only a few of the newer ones for discussion. While other methods, such as the history and physical examination, are still the cornerstone of accurate diagnosis, they cannot be reviewed in detail here. A history compatible with gallstones, cancer of the pancreas, a recent operation on the biliary tract, alcoholism, recent blood transfusions, or ingestion of drugs known to cause cholestatic jaundice would be of great help in the differential diagnosis of jaundice. Physical examination is likewise of primary importance, especially regarding the size of the liver and spleen, the palpability of the gallbladder, and the stigmata of cirrhosis of the liver. These aid in diagnosing and in the choice of proper tests for greater accuracy in the diagnosis.

Biochemical tests depend on the many synthetic and excretory functions of the liver and on the release of enzymes that occurs during cell destruction. Dr. Barrett will discuss those related to bilirubin metabolism. Unfortunately, biochemical tests are often confusing because of the mixture of bile duct obstruction and damage to the liver cells that is frequently the case in the jaundiced patient.

A liver biopsy specimen may be obtained at operation under direct vision, or by the transcutaneous route or a transjugular transhepatic route. The value and risks of obtaining specimens will not be discussed today.

Radiological examination includes the well-established upper gastrointestinal series and oral or intravenous cholecystography and cholangiography. Because of current great interest in the new radiological methods, our presentations will cover liver scanning, angiography, and transjugular transhepatic cholangiography.

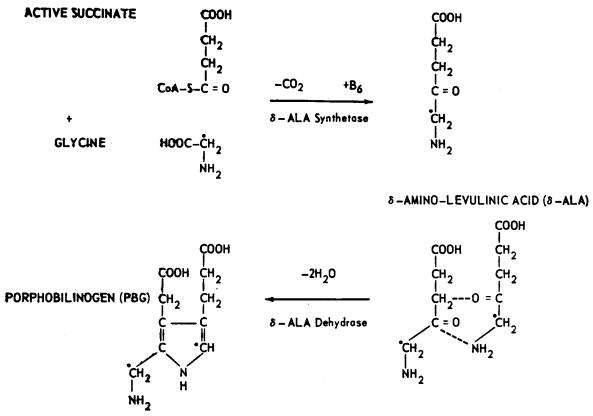

Chart 1.—The major steps in monopyrrole biosynthesis. The dots indicate the positions of the isotopic carbon atoms when glycine-2-C^{14} is used as a precursor.

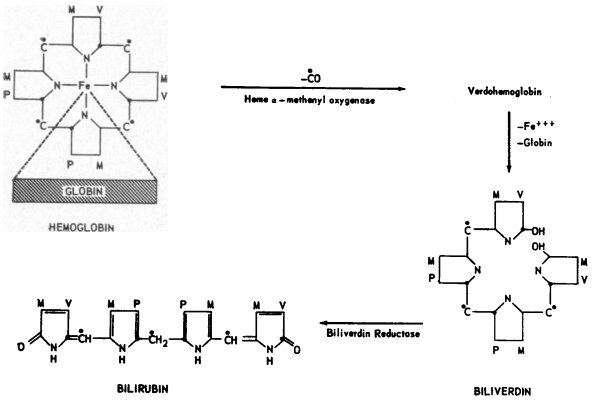

Chart 2.—The major steps in hemoglobin metabolism. Isotopic carbon atoms indicated by dots.

In addition to the case of cancer-derived obstructive jaundice presented by Dr. Johnson, we shall discuss two difficult problems in the field of obstructive jaundice: biliary atresia and sclerosing cholangitis.

Bilirubin Metabolism In Obstructive Jaundice

DR. PETER BARRETT (Division of Gastroenterology): The presence of jaundice has attracted man's interest for centuries, an interest reflected by the fact that two of the four humours of classical Greek medicine were bile, yellow and black. Today our approach is a little more sophisticated, but many questions remain and one of the most interesting concerns the disposition of bilirubin in obstructive jaundice. It is well known that, in the presence of complete obstruction (which the patient presented probably had) the serum bilirubin seldom exceeds 20 mg per 100 ml, yet it continues to be produced at a normal or even increased rate. I will return to this aspect of bilirubin metabolism presently.

In order to discuss bilirubin metabolism in the presence of extrahepatic obstruction, it is first necessary to review very briefly some aspects of normal bilirubin metabolism.

Charts 1 and 2 summarize the steps involved in the production of bilirubin. Hemoglobin is the best known hemoprotein, but the heme moiety is a critical portion of a variety of different enzymes, myoglobin, and the cytochromes. When these compounds are degraded, the iron is plucked from the cyclic molecule, and scission of the ring occurs at the alpha bridge carbon position, resulting in the release of carbon monoxide. It is worth emphasizing that one mole of carbon monoxide is produced for each mole of heme which is degraded, and the measurement of the rate of carbon monoxide production has proved to be a useful index of heme turnover.

Bilirubin is the major degradation product of heme in the body, and this pigment is rapidly cleared from the serum by the liver. For example, if a tracer dose of C^{14}-bilirubin is given to a normal person, less than 10 percent remains in the serum at the end of four hours.[1] Once the bilirubin enters the hepatocyte, it is probably bound to a specific protein during its journey to the endoplasmic reticulum, where conjugation of the molecule occurs.[4] Conjugated bilirubin is subsequently excreted into the bile canaliculus and then into the intestine.

The sequence of pathologic changes which occur in extrahepatic obstructive jaundice has been well described. In a typical case, the initial changes consist of cholestasis, infiltration of polymorphonuclear neutrophils and edema in the portal triads. With prolonged obstruction, the portal areas become enlarged with proliferating bile ducts, fibrous tissue, inflammatory cells, and histiocytes. Bile infarcts are pathognomonic of this condition, but are relatively uncommon and therefore of little assistance in the differential diagnosis of jaundice.

Using cytochemical techniques, an increased amount of alkaline phosphatase has been demonstrated in the bile canaliculi shortly after the onset of experimental obstruction, and the serum content of this enzyme begins to rise. It is of note that ligation of only one major hepatic bile duct will produce a rise in the serum alkaline phosphatase.

By contrast, in the presence of an otherwise normal liver, the same procedure will not lead to an elevation of the serum bilirubin, for there is adequate clearance by the non-obstructed liver. This concept is essential for an understanding of the disparity between the serum alkaline phosphatase and bilirubin which may be observed in the presence of focal metastatic disease or in the occasional case of blockage of the right or left hepatic duct by tumor or stone.[11]

The serum alkaline phosphatase determination is very useful in the differential diagnosis of jaundice, but there is a moderate amount of overlap between parenchymal and obstructive disease states. Consequently, one cannot be dogmatic about the presence or absence of obstruction on the basis of this test alone.

In the presence of common bile duct obstruction the intraductal pressure rises, and above a level of 23 mm of mercury the production of bile ceases and the serum bilirubin concentration begins to rise. The precise pathway by which bilirubin returns to the serum is still unsettled. It has been suggested that conjugated bilirubin might make its way from the bile canaliculus to the lymphatic system. However, experiments in dogs have shown that, although there is a sharp rise in the thoracic duct bilirubin concentration immediately following the ligation of the common bile duct, this elevation persists for only a few hours and then returns almost to normal despite persistent obstruction.[3] This suggests that lymphatic outflow is not a significant pathway for the return of bilirubin from the liver to the serum. Two possibilities remain: The conjugated bilirubin may return to the serum directly from the hepatocyte or, alternatively, it may be excreted into the bile canaliculus and then travel between the cells back to the sinusoid. This issue must still be considered controversial.[14]

Attempts have been made to differentiate parenchymal from obstructive jaundice on the basis of the ratio of direct to indirect bilirubin (that is, conjugated to unconjugated bilirubin); however, the two fractions are generally found to rise together in both types of jaundice and the ratio offers no assistance in the differential diagnosis.[21] The only situations in which this ratio is useful occur in patients with jaundice due to increased bilirubin production, as in hemolytic anemia, or in patients with metabolic defects such as Gilbert's syndrome, in which an elevation of the unconjugated fraction of bilirubin predominates.

Bilirubinuria occurs in patients with obstructive jaundice. The excreted pigment is the conjugated, water-soluble fraction and is thought to be excreted chiefly by a process of glomerular filtration.[19] However, as the amount which can be measured in the urine in the presence of extrahepatic obstruction usually represents less than 20 percent of the daily bilirubin production, it is necessary to invoke other pathways and mechanisms for the disposal of the remaining 80 percent. This leaves us with a perplexing situation: In a patient with complete obstruction, the bilirubin cannot be delivered into the gut, and only a small fraction can be found in the urine.

Recent studies in mutant rats that cannot conjugate and excrete bilirubin normally have shown that, after the infusion of radioactive bilirubin, most of the radioactivity appears in the bile, but as unidentified water-soluble compounds; very little material can be identified as bilirubin itself.[15] This demonstrates that alternate pathways of bilirubin degradation are present, at least in this species, and it is possible that similar mechanisms account for the disposition of bilirubin in the presence of obstructive jaundice in man.

It has been proposed that alternate pathways for bilirubin degradation occur in the endoplasmic reticulum, the site of many drug detoxification reactions. In this regard it is of note that in jaundiced patients the administration of glucocorticoids (compounds known to induce certain drug metabolizing enzymes) usually results in a fall in the serum bilirubin concentration. The decrease in the serum bilirubin is most pronounced in patients with hepatitis, and this fact has been utilized as an aid in the differential diagnosis of parenchymal and obstructive jaundice. In practice, however, the reliability of this test is uncertain, and it is seldom used.

Further research will provide a better understanding of the pathophysiology of obstructive jaundice and will allow improvement in the care of patients with this problem.

Angiography in Differential Diagnosis

DRS. JOSEPH RÖSCH* and RICHARD J. STECKEL (Department of Radiology): Angiography is a valuable technique in the differential diagnosis of obstructive jaundice.[2] It gives detailed information about pathologic processes involving the liver and

*Visiting Professor, Docent of Charles University, Prague, Czechoslovakia.

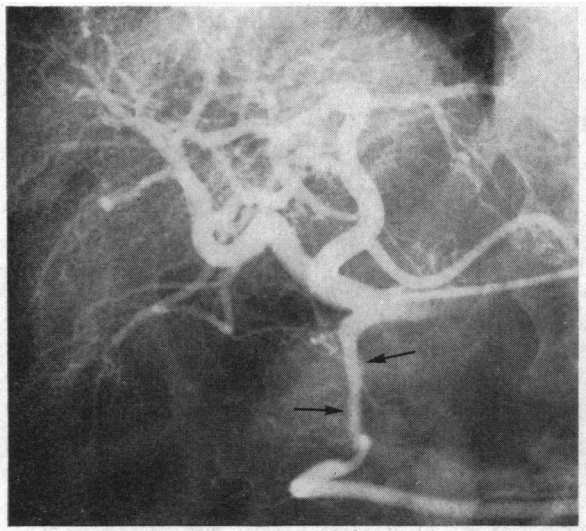

Figure 1.—Obstructive jaundice caused by pancreatic carcinoma. Hepatic arteriography; tumor infiltration of the gastroduodenal artery (arrows) and small pancreatic branches.

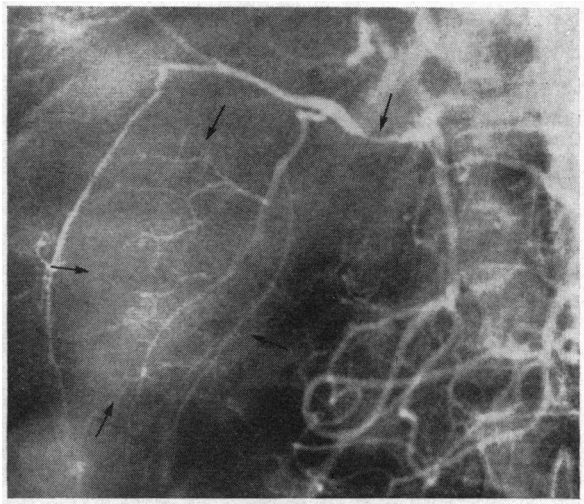

Figure 2.—Obstructive jaundice caused by carcinoma of the gallbladder spreading into the hepatic hilus. Superior mesenteric arteriography; arrows indicate tumor neovascularity occupying the entire gallbladder region and tumor infiltration of an aberrant hepatic artery.

individual organs in the subhepatic area, and often results in direct visualization of the lesion causing biliary obstruction. It is useful in demonstrating tumors of the pancreas,[7] gallbladder, bile ducts and liver (both primary and metastatic), and serves to differentiate them from non-neoplastic lesions. By determining the extent of a tumor and the secondary involvement of surrounding organs and vessels, angiography also contributes greatly to evaluation of tumor operability.

Selective studies of the celiac artery complemented by selective superior mesenteric studies, are the basic examinations used.[10] These procedures result in visualization of all organs in the upper abdomen and give a good impression of the portal circulation in the venous phase of the angiogram. For better evaluation of individual organs and increased diagnostic accuracy, superselective arteriography should be performed in questionable cases. Direct hepatic artery injection gives a good survey of the liver and gallbladder. Direct (superselective) gastroduodenal, dorsal pancreatic or inferior pancreaticoduodenal contrast injections are most suitable for diagnosis of disease in the pancreas or the duodenal papilla.[12]

Obstructive jaundice, whatever its cause, exhibits certain typical angiographic changes in the liver as a result of the cholestasis: because of the enlarged intrahepatic bile ducts, the hepatic vascular branches are narrowed and stretched, and the opacity of the liver in the capillary phase is irregular, with ribbon-shaped negative defects.[13] These liver changes, combined occasionally with faint visualization of an enlarged gallbladder, are usually the only pathologic angiographic findings in cases without tumor. By contrast, biliary obstruction caused by tumors exhibit certain additional angiographic changes, which are of crucial importance.

Pancreatic carcinoma (Figure 1) is diagnosed principally by tumor infiltration of vessels. The smaller pancreatic arteries are affected first. They become irregular and narrowed with indented outlines, and may even appear amputated. Later on, an enlarging tumor will also infiltrate the adjacent major vascular trunks—the gastroduodenal, hepatic and superior mesenteric arteries, and the portal vein. Tumor neovascularity is usually not striking, consisting only of very fine vessels, and neovascularity usually is absent in the scirrhous type of carcinoma. The infiltrative changes in the vessels are of greatest importance in the differential diagnosis: in inflammatory enlargement of the pancreas, there is only displacement and mild deformity of the pancreatic branches or surrounding arterial trunks, but never signs of tumor invasion of the vessels.

Cancer of the duodenal papilla, particularly in its infiltrative form, also invades the nearby arteries. Only the small branches of the pancreaticoduodenal arcades are usually affected, appearing irregularly narrowed or amputated. Superselective injection techniques are essential for evaluating these small branches.

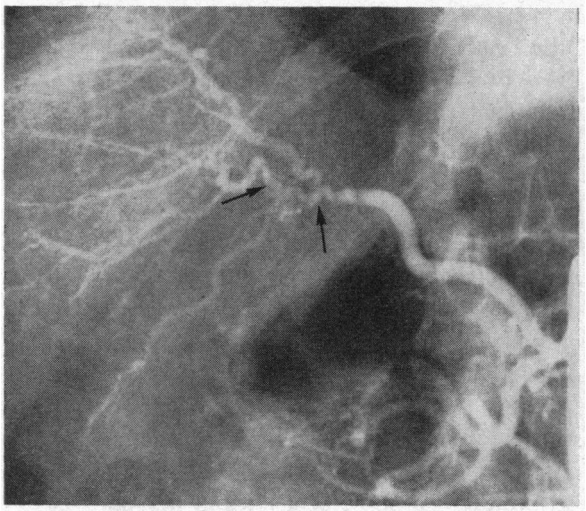

Figure 3.—Obstructive jaundice caused by carcinoma of the bile ducts in the liver hilus. Superior mesenteric arteriography; tumor infiltration of the aberrant hepatic artery and its main branches in the hilus (arrows).

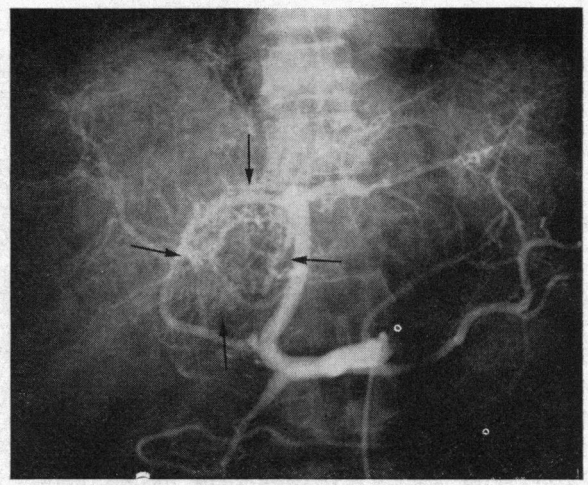

Figure 4.—Obstructive jaundice caused by primary hepatoma. Celiac arteriography; extensive tumor neovascularity in the hepatic hilus (arrows); infiltration of right hepatic branch, displacement of enlarged left hepatic branch.

Cancer of the gallbladder (Figure 2) exhibits tumor neovascularity as the main pathologic finding on angiography. The tumor vessels are irregular and sometimes straightened, and in other cases are tortuous and may form "vascular lakes." They are supplied primarily by the cystic artery and its branches. In cases with tumor infiltration into surrounding organs, the tumor vessels may acquire additional supply from the intrahepatic, duodenal or right colic arteries. A large tumor usually invades the adjacent vascular trunks, and the hepatic artery and the portal vein are most often affected.

Cancer of the extrahepatic bile ducts (Figure 3) is diagnosed by tumor infiltration of adjacent arteries, with the proper hepatic artery and its bifurcation usually affected. These arteries are irregularly narrowed and are often tortuous. With hepatic spread of the tumor, similar infiltrative changes are noted in the intrahepatic branches close to the liver hilus. There is also sometimes slight tumor neovascularity and tumor staining around the infiltrated vessels.

Primary hepatoma leading to obstructive jaundice (Figure 4) usually presents in a massive solitary form with perihilar localization. It is highly vascular and supplied by an enlarged hepatic artery. The tumor vessels are large and tortuous, forming bizarre vascular networks. Arteriovenous shunts may also be present, with filling of irregular vascular lakes. There is prominent "tumor staining," with the hepatoma becoming densely opacified in the capillary phase. Portal vein thrombosis is frequently visualized late in the angiogram, along with retrograde filling of a collateral venous circulation.

Liver metastases may have varying angiographic appearances, depending on their vascularity. Metastases from hypernephromas, thyroid or islet-cell carcinomas, hemangiosarcomas, and occasionally even colon carcinomas, may be highly vascular and may present with many irregular tumor vessels in the arterial phase, and with tumor "staining" of the metastatic deposits in the capillary phase of hepatic angiography. The angiographic diagnosis of poorly vascular or avascular metastases is based principally on deformity of the surrounding intrahepatic branches, and on filling defects in the liver parenchyma visible in the capillary phase.

In summary, angiography aids preoperatively in the differential diagnosis of obstructive jaundice of neoplastic origin. It demonstrates the tumor as well as its extent, and is of great assistance in evaluating potential operability.

Liver and Pancreatic Scanning

DR. MILO M. WEBBER (Department of Radiology): As far as definition of the images is concerned, what I have to show here is going to be a poor second to the radiographic procedures. However, the entire principle is relatively new and, I think, measured against radiography and the advances we have seen in the past 60 or 70 years is equivalent to radiography back in the 1910s or

TABLE 1.—*Liver Scanning Agents*

Agent	*Tracer*
Radiogold	Au^{198}
Rose bengal	I^{131}
Human serum albumin (microaggregates)	I^{131}
Human serum albumin (microaggregates)	Tc^{99m}
Radiotechnetium-sulfur colloid	Tc^{99m}
Indium colloid	In^{113}

1920s. I think we have a long way to go, but the future is there.

Two procedures, liver scanning and pancreatic scanning, were of special importance in the case presented earlier. Before discussing them briefly, I would like to mention that liver scanning is in a broad sense a UCLA development, in that the first papers published on the subject were those of Dr. Stirrett and his associates back in the early 1950s.[17]

The technique of scanning is different from the technique of x-ray radiology in that the patient himself, rather than an x-ray tube, is emitting the photons. We attempt to make radioactive the part of the patient that we are interested in visualizing. In liver scanning we are limited to a few agents; Table 1 lists some of the most commonly used. Radiogold-198, in use throughout the world, is listed first. Rose bengal attracted originally a great deal of interest and is still used to some extent; in fact, it has a unique application (to be discussed later) in cases of obstructive jaundice.

The earliest liver scanning was done with serum albumin tagged with radioiodine-131, not in a particulate form at all, which collected to a minimal extent in areas of tumor activity.[17] The type of scan obtained in the early days was unsatisfactory in comparison with what we are capable of obtaining today. Small particles of serum albumin, prepared by heating and shaking, when given intravenously are concentrated by the reticuloendothelial system throughout the liver and spleen. When the scan is made, the liver and the spleen are visualized. The albumin particles can be tagged with radioiodine,[18] as they are in most places, or with radiotechnetium-99m, a relatively new tracer which permits the use of much more radioactivity with much less radiation damage.

Radiotechnetium-99m-sulfur colloid is a relatively new agent which consists of small particles of sulfur that include technetium sulfide; it is also localized within the reticuloendothelial system of the liver.[9] And, finally, Indium-113m, a new tracer which, like radiotechnetium-99m, has a very short half-life (approximately 90 minutes), can be used in large doses and yields many photons yet delivers little destructive irradiation to the patient.[5] With these two agents the scan images appear to have fine detail, and we see things that we were unable to see with the older types of scanning techniques.

By the use of the techniques which involve uptake of tracer within the reticuloendothelial system we see the collection of cells that represent the active phagocytes of this system. Several patterns can be present in a normal person, and it is very difficult to say that one pattern is normal and another abnormal. In fact, there are probably 15 or so usual patterns; of those most commonly seen, we have selected four, shown in Figure 5, which represent what the liver scanning technique might be expected to show in a normal person.

Note that in some instances the left lobe is more prominent than in others; in Figure 5B it is almost separate—in fact, in some cases an actual cleft can be seen between the two lobes. The spleen shows up well at times, as in Figure 5C, where it is much more apparent than in 5A; the difference is due to the agent used (technetium-sulfur suspension in 5C, gold-198 in A). Another possible source of confusion is a Riedel's lobe extending from the tip of the right lobe.

In addition to the wide variation in the normal appearance of the liver, there is the problem of loss of detail due to the patient's breathing during the many minutes needed to perform a scan. There is also a limit to the size of the lesion that can be seen in the liver scan: it must be at least 2 to 3 cm in diameter (depending upon its location within the liver) for it to be discerned with certainty. If there are many small metastases scattered throughout the liver, we will be unable to see them. On the other hand, we can be sure to see large enough metastases, cysts or abscesses, even though we cannot really distinguish these processes from one another but see them all as areas of decreased tracer uptake. If they are too small, however, we may easily miss them.

Figure 6 is a good example of what might be seen in a patient with a tumor at the head of the pancreas, as in the case here presented. Note a light area, rather large, extending up from the hilar region of the liver, representing destruction of functioning reticuloendothelial cells throughout the liver in the region of the porta hepatis.

Figure 7 also shows the possible result of a tumor in the pancreas. The left lobe cannot be seen; its absence could represent that a tumor has

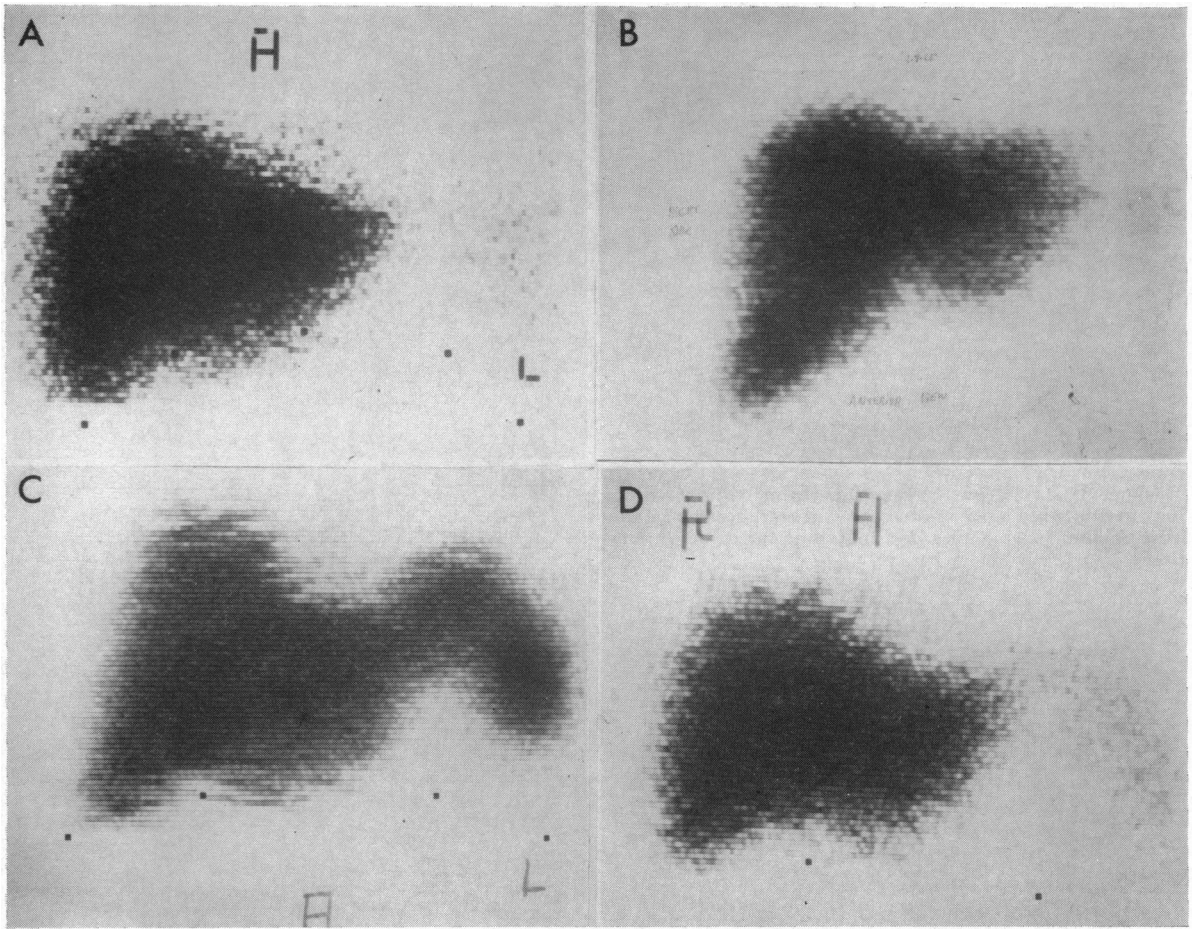

Figure 5.—Commonly encountered scanning configurations of the normal liver and spleen. Note that the spleen is usually not seen clearly. *A:* Gold-198 scan. *B, C, D:* Technetium-sulfur suspension scans; note prominent left lobe in *B* and clearly visualized spleen in *C*.

involved and destroyed it, especially if the presence of a mass in this region were confirmed radiographically or by physical examination.

Rose bengal can yield unique information for the diagnosis of obstructive jaundice. Upon ingestion, rose bengal is picked up by the parenchymal cells of the liver, excreted in the gallbladder, and then, if all is normal, passes out into the gastrointestinal tract to the duodenum. This excretion sequence is prevented by an obstruction. The rose bengal will be picked up by the liver, if the liver still has this capacity, but then the agent will gradually be released by the liver into the bloodstream, to be eventually excreted through the kidneys.

Figure 8 illustrates the usefulness of the rose bengal liver scan. There is essentially no uptake of technetium-sulfur colloid (Figure 8A) in the Kupfer cells of the liver. In the particular case illustrated the liver function was so impaired because of obstructive disease that most of the colloid is picked up in the spleen, the bone marrow, some in the liver, and some in the phagocytes of the lungs. Figure 8B shows a rose bengal scan in the same patient. The tracer is picked up initially in the liver and in the gallbladder, which is seen clearly; much of the tracer is then passed into the gastrointestinal tract, and a good deal of it can be seen in the bowel. This is a diseased liver, but there is no evidence of actual obstruction, although there is no question that the capacity to pick up a tracer such as technetium-sulfur colloid is much impaired.

Pancreatic scanning, in practice since about 1962, is based on the labeling of methionine (a precursor to pancreatic enzymes) with radioselenium-75. An uptake in the pancreas (Figure 9) can be seen in about 50 percent of the cases given the labeled methionine. If an uptake looks rela-

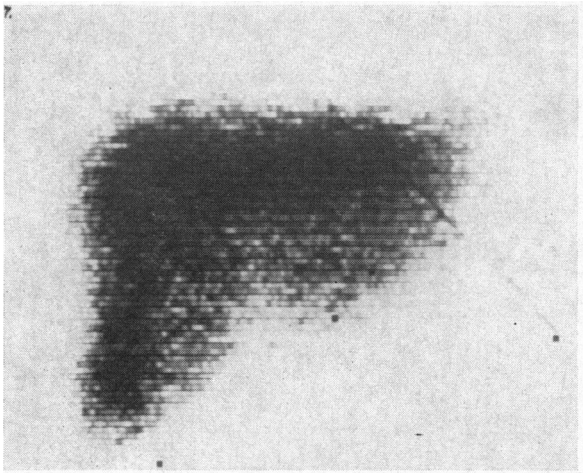

Figure 6.—Liver scan (technetium-sulfur colloid) showing questionable area of decreased tracer uptake in the hilar region, representing destruction of functioning liver tissue.

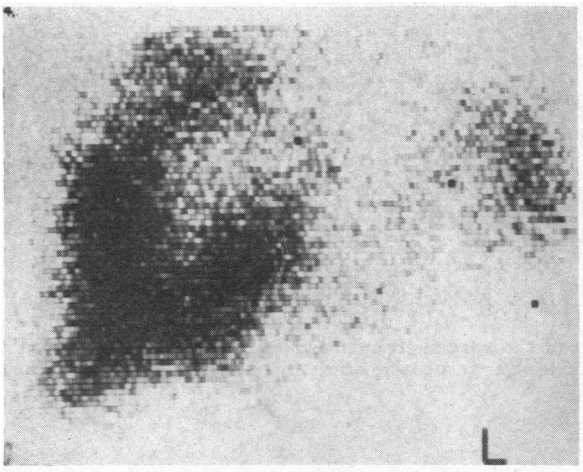

Figure 7.—Liver scan (technetium-sulfur colloid) showing destruction of the left lobe and of a portion of the right lobe due to malignancy.

tively normal in concentration and configuration (taking into account that we are in a very early stage in the understanding of the variations of the pancreas in man) the chances are that the organ is normal. On the other hand, failure to visualize it or the presence of areas of no uptake is a good indication of some problem with the pancreas. This is not a widely accepted technique; I think it has promise for the future. Some investigators have claimed it to be as good as angiography of the pancreas, but that, of course, depends upon the capability (and luck) of the person doing the angiography. Scanning is, however, nontraumatic and can be done with relative ease compared with current angiographic techniques.

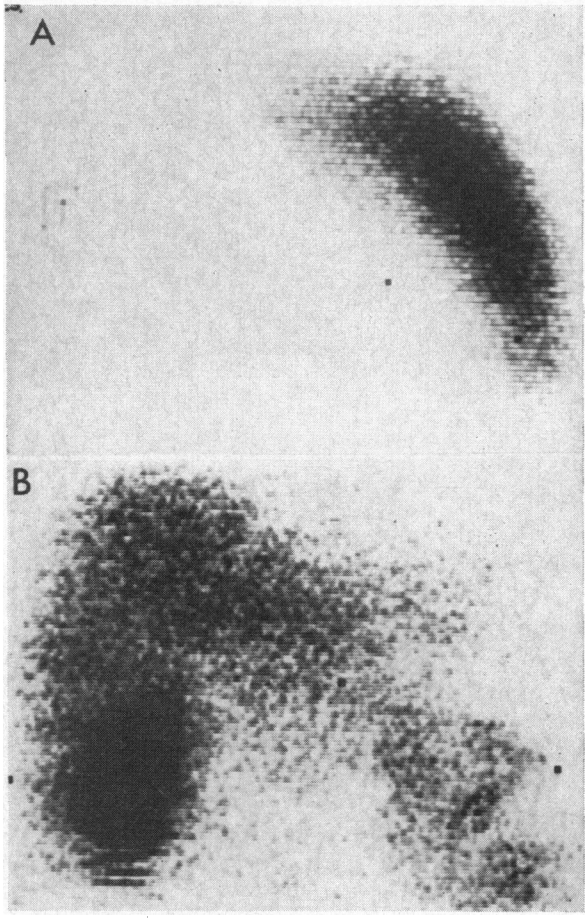

Figure 8.—*A:* Liver scan (technetium-sulfur colloid) showing no particulate uptake in the liver Kupfer cells, but only in the phagocytes of the spleen. *B:* Rose bengal scan on same patient, showing functioning of the parenchymal cells and discharge of the tracer into the gastrointestinal tract.

Transjugular Transhepatic Cholangiography

DR. MARTIN A. POPS (Department of Medicine): To start with an oversimplification: in cases of obstructive jaundice, the obstruction is surgically amenable where it resides exterior to the liver. But the clinical picture and laboratory tests can be identical to those obtained in cases where it is located within the liver, as it may be when cholestasis occurs secondary to infectious hepatitis or is caused by chlorpromazine or methyltestosterone. This has led in some instances to the mistaken performance of surgical operation in cases of cholestatic viral hepatitis, with great risk to the patient. Thus it is important to determine whether patients with apparent obstructive jaundice are surgically treatable.

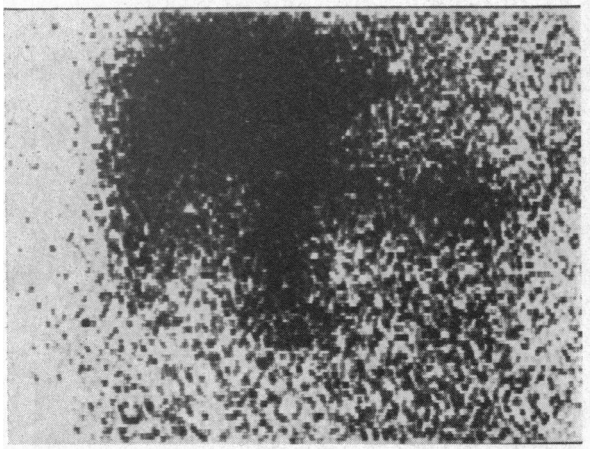

Figure 9.—Scan of the pancreas done with Se^{75}-labeled methionine.

The oldest technique (and the one that we still favor when possible) is visualization of the biliary tree by intravenous cholangiography. This depends on hepatic conjugation and excretion of an iodide introduced into the systemic circulation. With jaundice, however, liver function may well be compromised to the point where uptake and excretion of the opaque substance is suboptimal and visualization is not obtained. Direct cholangiography may then be considered. Three techniques are now in use.

The first method is, of course, to operate on the patient and do a cholangiogram at the operating table. Operative cholangiography has wide application, with obvious limitations. As our main topic is the preoperative evaluation of the jaundiced patient, we shall proceed to consider the other types of direct cholangiography.

Transhepatic cholangiography involves the injection of a dye directly into the biliary tree after lateral percutaneous puncture of the liver. The contrast agent fills the biliary system. In Figure 10, a gallstone totally occluding the common hepatic duct can be seen. The patient presented with jaundice and pruritus but no pain. The cholangiogram proved that in her case jaundice was amenable to surgical treatment.

Transhepatic cholangiography poses some problems, and the reports dealing with this method often stress the need for immediate surgical intervention should obstruction be found. One recognized complication is leakage of bile back through the hepatic puncture site into the peritoneal cavity, with resultant bile peritonitis.

The other reported complication of this procedure is hemoperitoneum. In performing transhepatic cholangiography the liver capsule is being punctured from the outside, so to speak. Having created a situation where either bile or blood can extravasate into the peritoneal cavity, most persons experienced with this method would like to be sure that the operating room is ready in case ductal obstruction is found.

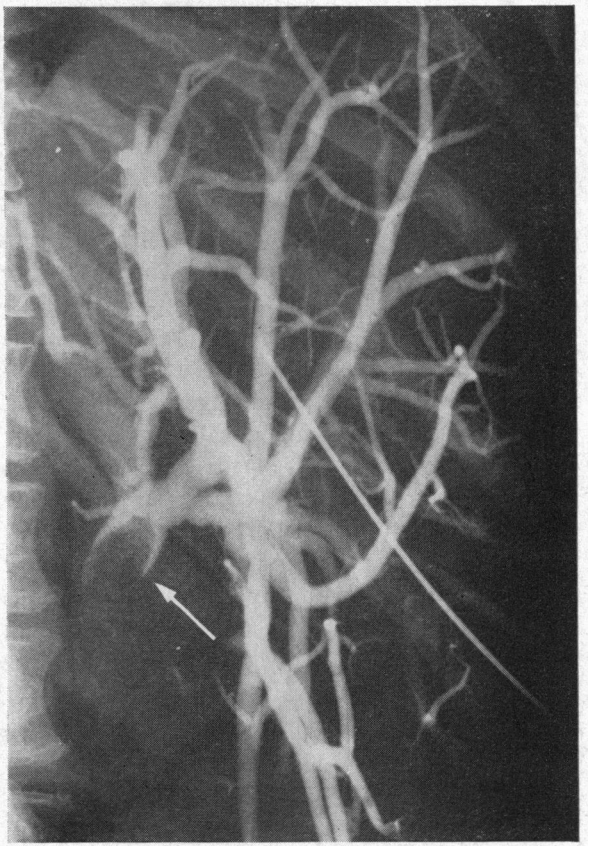

Figure 10.—Transhepatic cholangiogram demonstrating total occlusion of the common hepatic duct by calculus (arrow).

At UCLA, Drs. W. N. Hanafee and M. Weiner have recently devised a method of percutaneous cholangiography whereby the biliary system may be opacified without the necessity of hepatic capsule puncture. They found that straight-line access to the hepatic veins was obtainable by cannulation of the right internal jugular vein. A slightly curved long needle, adapted from trans-septal cardiac catheterization, can be passed into the liver via its venous system and thence into the hepatic parenchyma and finally into a biliary duct. The chances of successful visualization are, of course, increased if extrahepatic obstruction and secondary ductal dilatation are present. This technique may provide

an advantage over transhepatic cholangiography because the hepatic capsule is not punctured, thereby reducing or eliminating the risks of bile peritonitis and hemoperitoneum. Our experience over the past three years has tended to bear this out.

Figure 11 illustrates a transvenous (transjugular) cholangiogram done by the technique just described. It shows a common duct stricture in a man who presented with jaundice six years after cholecystectomy.

Figure 12 shows the radiographic studies in the case presented by Dr. Johnson. The upper gastrointestinal series shows some suggestive effacement and narrowing of the duodenal loop and some obliteration of the folds of the duodenum, suggesting a mass in the head of the pancreas. The cholangiogram reveals an enormously dilated intrahepatic ductal system. The arrow points to a sharp cut-off which we have come to recognize as characteristic of tumor. As was noted earlier, on surgical operation a fairly large carcinoma was found at the head of the pancreas.

Complications of transjugular cholangiography have included febrile episodes in several patients following the procedure and, in one case, frank Gram-negative sepsis with death. The threat of bacteremia and sepsis may be reduced by preprocedural preparation of the patient with appropriate antibiotics such as ampicillin or tetracycline. It would seem wise to employ antibiotics in this way, especially if there is history of episodes of cholangitis.

In summary, then, we have a new technique of direct cholangiography which may be very useful in diagnosis and planning of management for the patient with apparent obstructive jaundice. The complication of bile peritonitis and hemoperitoneum can be avoided, thus eliminating the necessity for immediate operation. The risk of bacteremia is probably the same or greater than with transhepatic cholangiography.

Obstructive Jaundice in Infants

DR. ERIC W. FONKALSRUD (Department of Surgery): Although carcinoma of the head of the pancreas and choledocholithiasis are unusual in infants and children, jaundice is nonetheless a common and serious problem in this age group. Of particular clinical importance (as in adults) is the separation of obstructive from nonobstructive jaundice. Pathologic jaundice usually appears during the first 36 hours after birth. When jaundice

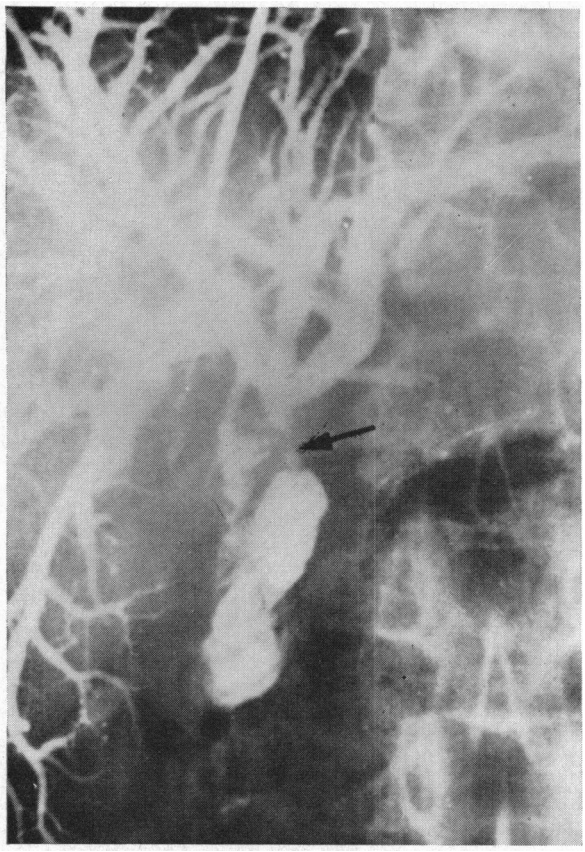

Figure 11.—Transjugular cholangiogram demonstrating severe stricture of the common hepatic duct (arrow).

persists beyond the second week of life, the likelihood is greater that it is of the obstructive type.

Obstructive jaundice may be identified by means of a combination of methods. The history and physical examination may indicate the possibility of the jaundice being caused by infection, isoimmunization, rubella, cystic fibrosis, or other nonobstructive conditions. The age at onset of the jaundice may be helpful in separating various types of nonobstructive jaundice, as is shown in Table 2, in which conditions are classified by whether jaundice first appeared before or after the seventh day of life. It seems that hepatitis in neonates is not an inflammatory condition similar to that in adults, but rather results from a congenital malformation of the hepatic cells.

Several conditions may produce nonobstructive jaundice in infants, with the onset of symptoms at various ages; these include conjugation deficiency, sepsis, concealed hemorrhage, galactosemia, spherocytosis, drug toxicity, and hypoxia. Jaundice may occur during the first week or as late as one or two months of age. Certain drugs

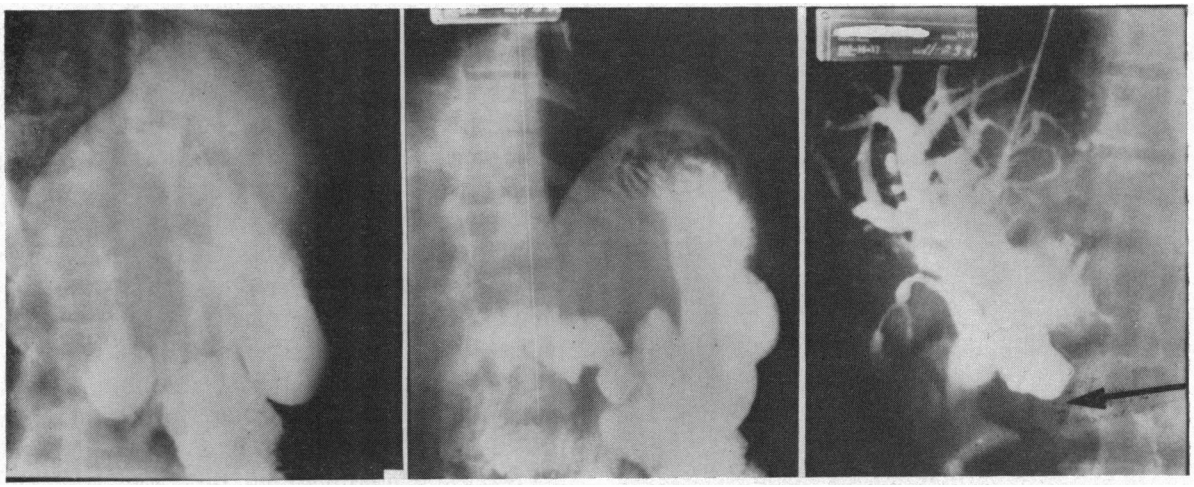

Figure 12.—***Left and center:*** **Upper gastrointestinal series showing suggestive effacement of the duodenal loop.** ***Right:*** **Transjugular cholangiogram demonstrating pronounced dilatation of intrahepatic ductal system; cutoff by tumor arising at the head of the pancreas is indicated by the arrow.**

TABLE 2.—***Classifying Characteristics of Nonobstructive Jaundice***

Appears Under 7 Days of Age
Icterus neonatorum
Isoimmunization (Rh and ABO)
Appears After 7 Days of Age
Hepatitis
Toxoplasmosis
Cytomegalic inclusion disease
Congenital syphilis
Familial nonhemolytic icterus
Cystic fibrosis
Pyloric stenosis

and sepsis may produce jaundice in an infant several months of age.

Various tests, such as the blood count, typing, Coombs' test, serology, urine galactose and examination for cytomegalic inclusion bodies, may be of help in identifying these causes of nonobstructive jaundice. Skull roentgenograms may identify toxoplasmosis as the cause of jaundice. The findings that are most helpful in the recognition of obstructive jaundice are acholic stools and biluria. An elevation in the direct serum bilirubin, absence of urobilinogen in the urine, and absence of I^{131} rose bengal excretion into the intestine are confirmatory evidence for the presence of obstructive jaundice.

Several forms of obstructive jaundice may occur in small infants. Congenital biliary atresia is the most common type in neonates, the incidence being 1 in 2,000 to 3,000 births. This malformation may be present in a variety of anatomical patterns, from atresia of the entire ductal system to either extrahepatic or intrahepatic ductal atresia. In the most commonly encountered form of this anomaly the extrahepatic ducts and gallbladder are atretic. In only a small number of infants does the intrahepatic ductal system empty into a dilated proximal extrahepatic duct which communicates with an atretic common bile duct. This is the only form of biliary atresia that may be corrected surgically by means of a choledochoenteric anastomosis, although the eventual prognosis depends upon the degree of cirrhosis that develops before operation.

Biliary hypoplasia is an uncommon malformation in which either extrahepatic or intrahepatic bile ducts are narrowed in localized areas, producing partial ductal obstruction and jaundice, sometimes at an early age. This condition is believed by many physicians to be a variant of giant cell hepatitis with narrow ducts. Many children with biliary hypoplasia live until adolescence, although cirrhosis and portal hypertension usually become evident and are progressive.

Choledochal cysts may become clinically symptomatic in infants as well as in children or adults. This congenital dilatation of the common bile duct produces partial biliary obstruction with resultant intermittent jaundice, fever, pain, and usually an abdominal mass. Such cysts should be recognized early and drained internally before severe cirrhosis develops. This is one of the most readily correctable forms of obstructive jaundice encountered in pediatric patients.

Most children with biliary atresia die within

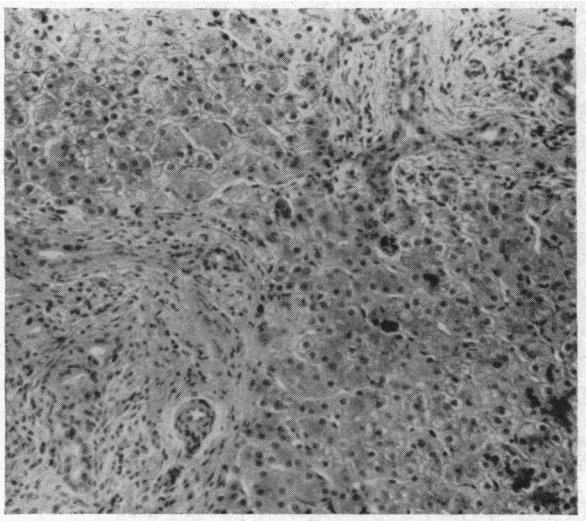

Figure 13.—Liver biopsy specimen from a 6-day-old infant with biliary atresia, showing moderate periportal fibrosis. This child subsequently underwent orthotopic liver homotransplantation and died with hepatic necrosis due to arterial thrombosis three weeks after transplantation.

the first two years of life (the average at 19 months), regardless of the type of therapy. Once the diagnosis is suspected and substantiated by the laboratory studies, a laparotomy with open liver biopsy is recommended. If the liver is firm, nodular and dark green, characteristic of biliary cirrhosis, the incision is extended and a thorough exploration of the hepatoduodenal ligament is undertaken in search of a dilated proximal duct, either extrahepatic or intrahepatic, which may be anastomosed to the small intestine. If the liver is soft, smooth and reddish brown, suggestive of hepatitis, a small catheter is placed into the gallbladder, and the wound is closed as quickly as possible to minimize the duration of anesthesia. A cholecystogram and cholangiogram are then performed with the patient awake. A well-visualized complete extrahepatic ductal system excludes the likelihood of biliary atresia. If the ductal system is not visualized and biopsy of a prepared speciman of liver is diagnostic of biliary atresia, laparotomy and extensive exploration of the biliary ductal system are subsequently performed. The importance of early biopsy and accurate identification of the occasional surgically correctable lesion early is emphasized by the case illustrated in Figure 13, which shows moderate cirrhosis in a specimen taken from an infant with biliary atresia at six days of age.

Because of the almost uniformly poor prognosis of children with biliary atresia, several experimental approaches have been studied to reduce the hyperbilirubinemia. The use of corticosteroids and cholestyramine to reduce the serum bilirubin, which was mentioned earlier in discussion of the management of adults with jaundice, has been of some value in infants with jaundice. Clinical attempts to reduce the serum bilirubin which is in equilibrium with lymph by external drainage of thoracic duct lymph have resulted in massive protein and fluid losses that make the procedure unfeasible for more than short periods. One child with biliary atresia was kept alive for approximately three months with the continued use of this treatment. At UCLA we have modified this approach by anastomosing the large lymphatic channels in the hepatoduodenal ligament to an isolated loop of small intestine in five children with biliary atresia, hoping to cause excretion of excess bilirubin and yet allow intestinal absorption of proteins and fluid. Although these procedures may lower the serum bilirubin temporarily, there is little evidence to suggest that the progression of the biliary cirrhosis is altered, and death usually occurs at approximately the same age as when the condition is untreated.

Perhaps the greatest hope for the future management of children with biliary atresia rests in liver homotransplantation, which has become increasingly successful during the past several years, and has been used in three patients in this hospital.

Sclerosing Cholangitis

DR. WILLIAM P. LONGMIRE, JR. (Department of Surgery): Sclerosing cholangitis is, fortunately, a rare disease and no one has a wide experience with it from which to draw specific conclusions. One of the largest series reported in the literature at this time concerns 42 cases collected by Warren and his associates[20] at the Lahey Clinic; the authors point out the almost uniformly unfavorable results of this disease.

There are two points that I would like to make in regard to this process, usually diagnosed at the time of operation for jaundice of an obstructive type in which a decided thickening and sclerosis of the wall of the common duct is found, a change that occurs in the submucosal layer with pronounced periductal inflammatory reaction about it. The extent of the condition may vary from a very mild sort of process to one that almost completely obliterates the lumen of the duct.

First, one must differentiate this process from

a primary bile duct carcinoma, and this can present some major problems, primarily because when performing a biopsy of the wall of the common duct the surgeon never likes to remove a really significant portion of the duct for fear of creating a permanent biliary fistula; hence the specimen that the pathologist frequently receives is not adequate to reach a definitive diagnosis.

Nevertheless, there are several points that can be made with regard to this differential diagnosis. In the first place, when dealing with sclerosing choledochitis, this is usually found to be a diffuse process that is apt to involve the entire extrahepatic biliary system. Not infrequently, changes will also be found inside the liver which are compatible with a primary biliary cirrhosis, or what we refer to as cholangiolitic hepatitis (to be further discussed later on).

On the other hand, in the case of carcinoma an operative cholangiogram will demonstrate a more localized area of constriction, and above that point of constriction a dilatation of the intrahepatic ductal system or a dilatation of some portion of the extrahepatic system if the process is localized to the lower portion of the duct. The point is that the sclerosing cholangitis is apt to be a diffuse process and the carcinoma apt to be localized, with dilatation above the point of obstruction in the case of carcinoma, and no dilatation above with the cholangitis.

As occasional exceptions to this, there are patients with a localized process, and these account for the rare case of sclerosing cholangitis in which some permanent cure may result.

In addition to this process alone, sclerosing cholangitis may also occur in combination with some other systemic diseases. Not infrequently, it occurs with ulcerative colitis, with retroperitoneal fibrosis, with sclerosing fibrosis in other anatomical sites; its relationship with these other diseases is not clear.

The other major point I would like to establish is that this is probably the same process that we identify as cholangiolitic hepatitis or primary biliary cirrhosis, affecting in this case first or most severely the extrahepatic portion of the biliary tract.

Cholangiolitic hepatitis occurs typically in the most proximal portion of the biliary secretory unit, while sclerosing cholangitis occurs more often in the major or extrahepatic ductal system. These processes frequently overlap. For example, in four of the 28 cases of cholangiolitic hepatitis that we have reported[6] from this institution the patient was thought to have a normal extrahepatic biliary tract at the time of the first exploration, but at subsequent exploration, a year or more later, all four were found to have extensive thickening and sclerosis of the extrahepatic system as the process seemed to extend. Turning the story around, practically all the patients reported upon by Warren and his associates[20] eventually died of biliary cirrhosis, so that there was an extension of the process along this line.

In relation to this disease and ulcerative colitis, 12 of the 42 patients in Warren's report had ulcerative colitis in association with the bile duct disease. Two of these patients made an excellent recovery, but ten did poorly, and five of them died of the disease. In nine of these ten patients biliary cirrhosis developed.

Sherlock[16] said that colectomy and antibiotics are of no benefit in the treatment of this particular type of disease; we therefore feel that this is probably not an infectious process but rather a systemic disorder of some type, possibly related to an immune or an allergic phenomenon. It is associated frequently with other disease processes of similar nature. It follows a rather unfavorable course in a majority of instances, and the various treatments of prolonged biliary drainage are probably ineffective in the majority of cases. Such treatment is possibly contraindicated, inasmuch as is provides a means or an avenue for secondary infection to enter and extend up the biliary tract. The use of steroids may be of some value in the very early cases if diagnosis can be made, and a short course of therapy along this line may be tried.

Discussion

DR. CLARKE: We have a few minutes for questions and discussion. First, I would like to say that we are delighted to have Professor Richard Welbourn from Hammersmith with us this month as a visiting professor in the Department of Surgery. I would like to invite Professor Welbourn to comment if he wishes.

DR. RICHARD WELBOURN (Royal Postgraduate Medical School of London, Hammersmith, England): I have been fascinated to listen to these papers on the diagnosis of obstructive jaundice. The liver scanning interested me very much. It is something which we, too, are doing; and, like you,

we are perhaps groping a bit in the early stages and not knowing what particular appearances really indicate.

The transjugular transhepatic cholangiography I found particularly interesting. I had not heard about this before. I shall certainly tell our radiologists at home about this, and ask them if they can help us, for it would be helpful in the type of patient on whom we now would have to do a puncture through the skin from the outside; and these procedures, of course, have to be done on the way to the operating theater, and not all these patients may need operation.

DR. SHERMAN M. MELLINKOFF: I wonder if I could ask Dr. Rösch if there is a characteristic appearance of the angiogram in cholangiolitic hepatitis or sclerosing cholangitis.

DR. RÖSCH: There are changes secondary to periportal infiltration, liver enlargement or liver atrophy, and cirrhosis; but there is no typical angiographic appearance of sclerosing cholangitis.

DR. LONGMIRE: I would like to ask Dr. Johnson why the bypass operation did not cure the jaundice in the case presented.

DR. JOHNSON: I could not tell from the chart. I do not know.

DR. LONGMIRE: It seems to me that there might be two possibilities. One is that the gallbladder was used in the decompression, and the tumor may have involved the junction between the cystic and the common ducts, thereby obstructing the channel of decompression; such a tumor extension frequently occurs and is one of the reasons that a cholecystojejunostomy is often not a satisfactory operation for decompression. The other explanation would be that intrahepatic disease was so extensive that the patient's jaundice would not be relieved even though the extrahepatic ducts were decompressed.

REFERENCES

1. Barrett PVD, Berk PD, Menken M, et al: Bilirubin turnover studies in normal and pathologic states using C^{14}-bilirubin. Ann Intern Med 68:355-377, 1968

2. Boijsen E, Reuter SR: Combined percutaneous transhepatic cholangiography and angiography in the evaluation of obstructive jaundice. Amer J Roentgen 99:153-161, 1967

3. Bollman JL: Bile pigments in blood, lymph and bile, in the course of experimental bile stasis, *In* Brauer RW (Ed): Liver Function; A Symposium on Approaches to the Quantitative Description of Liver Function. Washington DC, American Institute of Biological Sciences Publication No 4, 1958, pp 291-297

4. Gartner LM, Arias IM: Formation, transport, metabolism and excretion of bilirubin. New Eng J Med 280:1339-1345, 1969

5. Goodwin DA, Stern HS, Wagner HN Jr, et al: A new radiopharmaceutical for liver scanning. Nucleonics 24(11):65, 68, 1966

6. Longmire WP Jr, Joseph WL, Levin PM, et al: Diagnosis and treatment of cholangiolitic hepatitis (primary biliary cirrhosis). Ann Surg 162:356-365, 1965

7. Lunderquist A: Angiography in carcinoma of the pancreas. Acta Radiol [Ther] (Stockholm) Suppl 235:1-143, 1965

8. Moynihan B: Abdominal Operations, Vol II (4th ed revised), Philadelphia, WB Saunders Company, 1926, p 528

9. Patton DD, Garcia EN, Webber MM: Simplified preparation of technetium 99m sulfide colloid for liver scanning. Amer J Roentgen 97:880-885, 1966

10. Pollard JJ, Nebesar RA: Abdominal angiography. New Eng J Med 279:1093-1099, 1968

11. Posen S: Alkaline phosphatase. Ann Intern Med 67:183-203, 1967

12. Rösch J: Roentgenology of the Spleen and Pancreas. Springfield, Charles C Thomas, Publisher, 1967

13. Rösch J, Grollman JH, Steckel RJ: Arteriography in the diagnosis of gallbladder disease. Radiology 92:1485-1491, 1969

14. Rouiller C, Jézéquel A-M: Electron microscopy of the liver, *In* Rouiller C (Ed): The Liver; Morphology, Biochemistry, Physiology; Vol I. New York, Academic Press, 1963, pp 195-264

15. Schmid R, Hammaker L: Metabolism and disposition of C^{14}-bilirubin in congenital nonhemolytic jaundice. J Clin Invest 42:1720-1734, 1963

16. Sherlock S: Diseases of the Liver and Biliary System. (3rd edition) Oxford, Blackwell Scientific Publications, 1963, p 353

17. Stirrett LA, Yuhl ET, Libby RL: The hepatic radioactivity survey. Radiology 61:930-934, 1953

18. Taplin GV, Johnson DE, Dore EK, et al: Suspensions of radioalbumin aggregates for photoscanning the liver, spleen, lung and other organs. J Nucl Med 5:259-275, 1964

19. Wallace DK, Owen EE: An evaluation of the mechanism of bilirubin excretion by the human kidney. J Lab Clin Med 64:741-755, 1964

20. Warren KW, Athanassiades S, Monge JI: Primary sclerosing cholangitis; a study of 42 cases. Amer J Surg 111:23-38, 1966

21. Zieve L, Hill E, Hanson M, et al: Normal and abnormal variations and clinical significance of the one-minute and total serum bilirubin determinations. J Lab Clin Med 38:446-469, 1951